Non-Technical Abstract

Prostate cancer is the second leading cause of cancer death in men in the United States, with over 39,000 deaths in 1998. The incidence of this cancer has increased dramatically over the past 25 years, and this has been attributed in part to improvements in screening for elevated prostate-specific antigen (PSA). While elevated PSA levels are sometimes a natural phenomena of aging, or of other physiological states, they continue to be the most useful marker for malignant disease

If prostate cancer is caught early it can often be cured, but if the disease metastasizes and continues to progress, current first-line chemotherapy is not generally curative, and therapy is usually aimed at palliation and pain control using a variety of agents. However, if patients fail these regimens, at present, there is no further therapy that can be offered. New therapeutic modalities are therefore actively being sought for these patients.

The trial proposed here is based on a new approach to treatment of prostate cancer. Specifically it is aimed at patients in whom the cancer has spread, and is based on the use of a genetically engineered virus which is injected into the bloodstream destroys the metastatic cancer cells as identified by the presence of PSA on their surface

The technology begins with the common cold virus known as adenovirus. Calydon has altered this virus by injecting it with promoter and enhancer elements cloned from the human PSA gene. As a result of this engineering, Calydon's new therapeutic, called ARCA™ (Attenuated Replication Competent Adenovirus), reproduces in the prostate cancer cells (or those cells containing PSA) causing cancer cell death. Conversely, ARCA affects a minute number of cells that do not contain PSA (10,000:1) thus limiting the death of non-cancerous cells.

On a preclinical level, this technology showed promise. Starting in 1996, in experiments in laboratory mice, a single injection of Calydon's viral therapeutic CN706, caused implanted tumors to shrink on average by more than 80 percent. At the same time, PSA dropped to undetectable levels. A dose-finding experiment in the same animal studies showed increasing tumor shrinkage as the dose of CN706 was increased. As measured through physical examinations and through biodistribution and toxicology studies, no significant side effects appeared in the treated animals. In addition, the cancer did not reappear.

Human studies on the first generation virus CN706 began in 1997 at the Johns Hopkins University Oncology Center. This study showed promising results when virus was injected directly into the prostate of patients with localized disease. A second generation of the ARCA™ virus, called CV787, was developed by Calydon in 1998. In animal studies, this new product showed much higher effectiveness in destroying cancer cells, while maintaining a record of insignificant negative side effects.

The proposed clinical study CV787-9902 is a multi-center, open-label, dose finding study of CV787 adenovirus in patients with hormone refractory metastatic prostate cancer.

The primary objectives of the study are to determine the safety, tolerance, and maximum tolerated dose (MTD) of CV787 administered intravenously to patients with metastatic hormone refractory prostate cancer. Secondary objectives are to evaluate the PSA response rates, duration, and time to progression in these patients; to evaluate other clinical efficacy responses

observed; to evaluate the systemic pharmacokinetics of CV787 administered intravenously; and to monitor the immune response to CV787 administered intravenously.

Up to 48 patients will participate in this study. Patients will receive treatment intravenously at one of up to eight dose levels (A - H), each containing three to six patients .

Following screening, which will include patient history, physical exam, adenovirus antibody levels, lab tests (including PSA), tumor assessment by CT and/or MRI, bone scan, and other relevant assessments, patients will be assigned to a treatment cohort by Calydon, and enrolled into the study.

CV787 will be administered by i.v. infusion in 10 ml volume over 10 minutes. Patients will then be observed overnight in the hospital or similar facility, and followed weekly for one month after treatment, then at 2, 3, 4, 6, 9, 12, 15, 18, 21, and 24 months.

PSA response or progression will be assessed by PSA levels at the above mentioned times. For measurable lesions, tumor response will be assessed by CT or MRI, performed at visits $\geq$ 2 months.

Safety will be assessed by monitoring hematology, coagulation, serum chemistry, and urinalysis laboratory studies, physical examinations, serial PSAs, International Prostate Symptom Scores (PSSs), toxicity scores, and adverse events.

The immune response to CV787 will be assessed by monitoring for the development of antibodies to the virus. Systemic bioavailability and biodistribution will be determined by examining serial plasma samples for CV787.